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EXAMINER: SCHEINER, L

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DATE MAILED: 02/15/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 10/27/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-11, 14, 27-29, 31-34 & 36-51 are pending in the application.
   Of the above, claims 1-11, 14, 27-29, 31-34 & 36-39 are withdrawn from consideration.
2. ☑ Claims 12, 13, 15-26, 30 & 35 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 40-51 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 40-51 are rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40-51 are vague and indefinite in their recitation of "DNA for use in securing expression", "selected from among", "wherein one or more cysteine residues is deleted or replaced by another amino acid", "a polypeptide of subpart (a) or (b) wherein one or more cysteine residues is deleted or replaced by another amino acid", "a polypeptide of subpart (a) or (b) wherein one or more tyrosine residues is replaced by phenylalanine", and "a polypeptide of any of subparts (a), (b), (c) or (d), lacking residues -26 through -1, and having a methionyl residue at position -1", and/or "has at least one cysteine residue replaced by an amino acid selected from alanine and serine". What does "for use in securing expression mean"? Do applicants intend that the DNA encodes the polypeptide(s) of figure 2? With regard to the method claims, do applicants intend co-transfection? "Selected from among" is improper Markush language. Which

cysteine residues are replaced? Which amino acids are they replaced with? Which cysteine residues are deleted? Which tyrosine residues are replaced? Which cysteine residues are replaced with alanine or serine. Attention is directed to Ex parte Tanksley (26 USPQ2d 1384) wherein the Board noted that, under 35 USC 112, second paragraph, the claims must be so definite as to allow their comparison with the available art and must also make it possible for the public to determine from the claims what it is they comprehend. It is asserted that a member of the public would not know what is intended by that which is claimed.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Specific basis is lacking in the specification for the recitation of "wherein one or more cysteine residues is deleted or replaced by another amino acid". Thus, the recitation is considered to be new matter. Moreover, applicants point to page

11 for support of their newly amended claims, however, page 11, at lines 21-21, merely sets forth that the cysteine residues may be replaced by alanine or serine. That is, the examiner cannot find support for the deleted cysteine residues or for the replacement of any cysteine residues by any amino acid. Please see MPEP 608.04 and 706.03(o).

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure.

The scope of the claims is broader than the enablement provided by the specification. That is, variants of the instant enzyme inhibitor are claimed, however, the specification fails in teaching specific substituted or deleted polypeptides (or DNAs which encode said polypeptides) having the claimed characteristics. No guidance is provided as to which cysteine residues of the disclosed polypeptide can be modified without changing the activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the large number of polypeptides broadly encompassed by the claims. Predictability of which changes can be tolerated in a protein's amino acid sequence while retaining similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the

proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (see the whole publication of Bowie et al. 1990. Science, Vol 247, pp. 1306-1310, particularly p. 1306 and column 2 of p. 1308).

While recombinant and mutagenesis techniques are known and it is known that some proteins can tolerate a number of amino acid substitutions (i.e. predominantly in non-conserved amino acids), the positions within the protein's sequence where such amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited and such modifications are unpredictable in the absence of further guidance. Other positions in the sequence of such proteins are **critical** to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in binding, catalysis or other activity and in providing the correct three-dimensional spacial orientation of binding and/or catalytic sites, and one skilled in the art would expect any tolerance of a given protein to modification to decrees with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved

and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed DNAs encoding the polypeptide(s), for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation.

While enablement can be supported even if some experimentation is required, such experimentation must be merely routine and if the results to be obtained are unpredictable the experimentation is not routine, but rather **undue**. Applicants have not taught where the critical cysteine residues are in the instant polypeptide or related polypeptides having the same activity nor what amino acids are conserved in the particular claimed polypeptides nor the structural requirements for producing compounds of similar activity. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). Recently, in Ex parte Maizel (27 USPQ2d 1662), the Board considered that claims encompassing such biologically functional equivalents were analogous to a single means claim and as such were more broad than the disclosure which disclosed only a single specific DNA segment known to the inventor. Such is the case here in which the specification is considered enabling only for claims limited to the specific nucleic acid sequence given in Figure 2.

Claims 40-51 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laurie Scheiner whose telephone number is (703) 308-1122.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM 1 Fax Center number is (703) 305-7939.

LAS
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